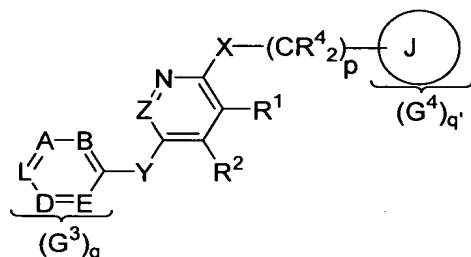


WE CLAIM:

1. A compound having the generalized structural formula

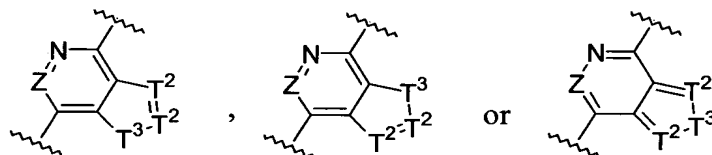


5

wherein

$R^1$  and  $R^2$

together form a bridge containing two  $T^2$  moieties and one  $T^3$  moiety, said bridge, taken together with the ring to which it is attached, forming a bicyclic of structure



10

wherein

each  $T^2$  independently represents N, CH, or  $CG^1$ ; and  $T^3$  represents S, O,  $CR^4G^1$ ,  $C(R^4)_2$ , or  $NR^3$ ;

and wherein

15

$G^1$  is a substituent independently selected from the group consisting of

20

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;

25

- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- 5      • carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- 10      • N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- 15      • carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- 20      • -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- 25      • -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- 30      • -NO<sub>2</sub>;
- -CN;

- amidino;
- guanidino;
- sulfo;
- -B(OH)<sub>2</sub> ;
- 5      • optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted saturated heterocyclalkyl;
- optionally substituted partially unsaturated heterocyclyl;
- 10     • optionally substituted partially unsaturated heterocyclalkyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- 15     • optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub> ;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup> ;
- 20     • -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>

R<sup>3</sup> is H or lower alkyl;

R<sup>6</sup> is independently selected from the group consisting of

- 25      • H;
- alkyl;
- cycloalkyl;
- optionally substituted aryl; and
- optionally substituted aryl lower alkyl;
- 30      • lower alkyl-N(R<sup>3</sup>)<sub>2</sub> ; and
- lower alkyl-OH;

R<sup>4</sup> is H, halogen, or lower alkyl;

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and  $\text{NR}^3$ ;

5

Y is selected from the group consisting of

- lower alkylene;
- $-\text{CH}_2-\text{O}-$  ;
- $-\text{CH}_2-\text{S}-$  ;
- 10 •  $-\text{CH}_2-\text{NH}-$  ;
- $-\text{O}-$  ;
- $-\text{S}-$  ;
- $-\text{NH}-$  ;
- $-(\text{CR}^4_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CR}^4_2)_s-$ ;
- 15 •  $-(\text{CR}^4_2)_n-\text{C}(\text{G}^2)(\text{R}^4)-(\text{CR}^4_2)_s-$  ;

wherein

n and s are each independently 0 or an integer of 1 – 2; and

$\text{G}^2$  is selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CON}(\text{R}^6)_2$ , and  $-\text{CH}_2\text{N}(\text{R}^6)_2$  ;

20

- $-\text{O}-\text{CH}_2-$  ;
- $-\text{S}(\text{O})-$  ;
- $-\text{S}(\text{O})_2-$  ;
- $-\text{SCH}_2-$  ;
- $-\text{S}(\text{O})\text{CH}_2-$  ;
- 25 •  $-\text{S}(\text{O})_2\text{CH}_2-$  ;
- $-\text{CH}_2\text{S}(\text{O})-$  ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

25

Z is  $\text{CR}^4$  or N;

30

q is 0, 1, or 2;

$\text{G}^3$  is a monovalent or bivalent moiety selected from the group consisting of:

- lower alkyl;
- $-NR^3COR^6$ ;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- 5     •  $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- $-OCOR^6$ ;
- 10    •  $-COR^6$ ;
- $-CO_2R^6$ ;
- $-CH_2OR^3$ ;
- $-CON(R^6)_2$ ;
- $-S(O)_2N(R^6)_2$ ;
- 15    •  $-NO_2$ ;
- $-CN$ ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- 20    • optionally substituted partially unsaturated heterocyclyl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- 25    •  $-S(O)_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-OCON(R^6)_2$ ;
- $-NR^3CO_2R^6$ ;
- $-NR^3CON(R^6)_2$ ; and
- bivalent bridge of structure  $T^2=T^2-T^3$
- 30                 wherein
- each  $T^2$  independently represents N, CH, or  $CG^3$ ; and

$T^3$  represents S, O,  $CR^4G^{3'}$ ,  $C(R^4)_2$ , or  $NR^3$ ; wherein

$G^{3'}$  represents any of the above-defined moieties  $G^3$  which are monovalent; and

the terminal  $T^2$  is bound to L, and  $T^3$  is bound to D, forming a 5-membered fused ring;

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH; and

with the provisos that

a) the total number of N atoms in the ring containing A, B, D, E, and L is 0, 1, 2, or 3; and

b) when L represents CH and any  $G^3$  is a monovalent substituent, at least one of A and D is an N atom; and

c) when L represents CH and a  $G^3$  is a bivalent bridge of structure  $T^2=T^2-T^3$ , then A, B, D, and E are also CH;

J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl;

$q'$  represents the number of substituents  $G^4$  on ring J and is 0, 1, 2, 3, 4, or 5, and

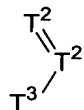
$G^4$  is a monovalent or bivalent moiety selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;

- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- 5      • hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- 10     • halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- 15     • hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- 20     • -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- 25     • halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- 30     • -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;

- -NO<sub>2</sub> ;
- -CN;
- amidino;
- guanidino;
- 5    • sulfo;
- -B(OH)<sub>2</sub> ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- 10   • optionally substituted partially unsaturated heterocyclyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- 15   • optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub> ;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup> ;
- 20   • -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub> ; and
- fused ring-forming bivalent bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

a)



25

wherein

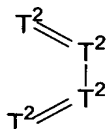
each T<sup>2</sup> independently represents N, CH, or CG<sup>4'</sup>;T<sup>3</sup> represents S, O, CR<sup>4</sup>G<sup>4'</sup>, C(R<sup>4</sup>)<sub>2</sub>, or NR<sup>3</sup>; whereinG<sup>4'</sup> represents any of the above-defined moieties G<sup>4</sup> which are monovalent; and

30

binding to ring J is achieved via terminal atoms T<sup>2</sup> and T<sup>3</sup>;

b)





wherein

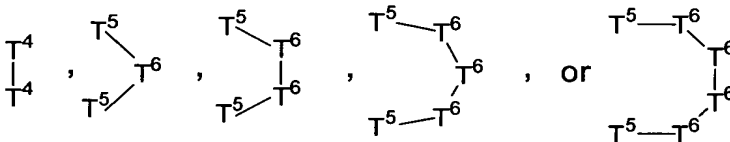
each  $T^2$  independently represents N, CH, or  $CG^{4'}$ ; wherein

$G^{4'}$  represents any of the above-defined moieties  $G^4$  which are monovalent; and

with the proviso that a maximum of two bridge atoms  $T^2$  may be N ; and

binding to ring J is achieved via terminal atoms  $T^2$ ; and

c)



wherein

each  $T^4$ ,  $T^5$ , and  $T^6$  independently represents O, S,  $CR^4G^{4'}$ ,  $C(R^4)_2$ , or  $NR^3$ ; wherein

$G^{4'}$  represents any of the above-defined moieties  $G^4$  which are monovalent; and

binding to ring J is achieved via terminal atoms  $T^4$  or  $T^5$  ;

with the provisos that:

- i) when one  $T^4$  is O, S, or  $NR^3$ , the other  $T^4$  is  $CR^4G^{4'}$  or  $C(R^4)_2$  ;
- ii) a bridge comprising  $T^5$  and  $T^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and
- iii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

when  $G^4$  is an alkyl group located on ring J adjacent to the linkage  $-(CR^4)_p-$ , and X is  $NR^3$  wherein  $R^3$  is an alkyl substituent, then  $G^4$  and the alkyl substituent  $R^3$  on X may be joined to form a bridge of structure  $-(CH_2)_{p'}$  - wherein  $p'$  is 2, 3, or 4, with the proviso that the sum of p and  $p'$  is 2, 3, or 4, resulting in formation of a nitrogen-containing ring of 5, 6, or 7 members;

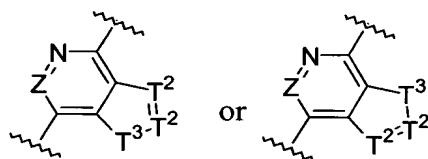
and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^3$  or  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 – 7 ring atoms;
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy,  $-CO_2R^3$ ,  $-CHO$ ,  $-CH_2OR^3$ ,  $-OCO_2R^3$ ,  $-CON(R^6)_2$ ,  $-OCON(R^6)_2$ ,  $-NR^3CON(R^6)_2$ , nitro, amidino, guanidino, mercapto, sulfo, and cyano; and
- when any alkyl group is attached to O, S, or N, and bears a hydroxyl substituent, then said hydroxyl substituent is separated by at least two carbon atoms from the O, S, or N to which the alkyl group is attached.

2. A compound of claim 1 wherein

$R^1$  and  $R^2$

together form a bridge containing two  $T^2$  moieties and one  $T^3$  moiety, said bridge, taken together with the ring to which it is attached, forming a bicyclic of structure



wherein

each  $T^2$  independently represents N, CH, or  $CG^1$ ; and

$T^3$  represents S, O,  $CH_2$ , or  $NR^3$ ;

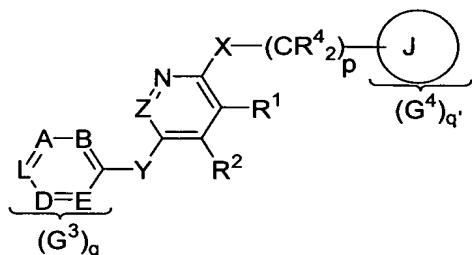
with the proviso that when  $T^3$  is O or S, at least one  $T^2$  is CH or  $CG^1$ .

3. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

4. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermiability processes, comprising administering to said mammal an amount of a compound of claim 1 which is effective to treat said condition.

5. The method of claim 4, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

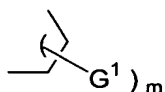
6. A compound having the generalized structural formula



wherein

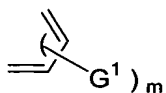
$R^1$  and  $R^2$  :

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



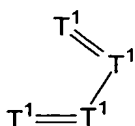
wherein binding is achieved via the terminal carbon atoms;

- iii) together form a bridge of structure



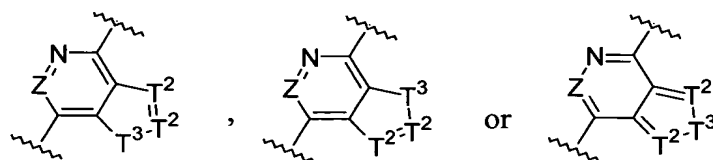
wherein binding is achieved via the terminal carbon atoms;

- iv) together form a bridge of structure



wherein one or two ring members  $T^1$  are N and the others are CH or  $CG^1$ , and binding is achieved via the terminal atoms; or

- v) together form a bridge containing two  $T^2$  moieties and one  $T^3$  moiety, said bridge, taken together with the ring to which it is attached, forming a bicyclic of structure



wherein

each  $T^2$  independently represents N, CH, or  $CG^1$ ; and  
 $T^3$  represents S, O,  $CR^4G^1$ ,  $C(R^4)_2$ , or  $NR^3$ ;

and wherein

m is 0 or an integer 1 – 4; and

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;

- lower alkoxy carbonyl-substituted alkyl;
- phenyl lower alkoxy carbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- 5      • N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- 10     • carboxy-substituted alkylamino;
- lower alkoxy carbonyl-substituted alkylamino;
- phenyl-lower alkoxy carbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- 15     • -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- 20     • -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- 25     • -NO<sub>2</sub>;
- -CN;
- amidino;
- guanidino;
- sulfo;
- 30     • -B(OH)<sub>2</sub>;
- optionally substituted aryl;

- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted saturated heterocyclalkyl;
- optionally substituted partially unsaturated heterocyclyl;
- 5      • optionally substituted partially unsaturated heterocyclalkyl;
- $-\text{OCO}_2\text{R}^3$ ;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
- 10      • optionally substituted heteroarylalkyloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-\text{CHO}$ ;
- $-\text{OCON}(\text{R}^6)_2$ ;
- $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- 15      •  $-\text{NR}^3\text{CON}(\text{R}^6)_2$

$\text{R}^3$  is H or lower alkyl;

$\text{R}^6$  is independently selected from the group consisting of

- 20      • H;
- alkyl;
- cycloalkyl;
- optionally substituted aryl; and
- optionally substituted aryl lower alkyl;
- 25      • lower alkyl- $\text{N}(\text{R}^3)_2$ ; and
- lower alkyl-OH;

$\text{R}^4$  is H, halogen, or lower alkyl;

30      p is 0, 1, or 2;

X is selected from the group consisting of O, S, and  $\text{NR}^3$ ;

Y is selected from the group consisting of

- lower alkylene;
- -CH<sub>2</sub>-O- ;
- 5      • -CH<sub>2</sub>-S- ;
- -CH<sub>2</sub>-NH- ;
- -O- ;
- -S- ;
- -NH- ;
- 10      • -(CR<sup>4</sup><sub>2</sub>)<sub>n</sub>-S(O)<sub>p</sub>-(5-membered heteroaryl)-(CR<sup>4</sup><sub>2</sub>)<sub>s</sub>-;
- -(CR<sup>4</sup><sub>2</sub>)<sub>n</sub>-C(G<sup>2</sup>)(R<sup>4</sup>)-(CR<sup>4</sup><sub>2</sub>)<sub>s</sub>- ;

wherein

n and s are each independently 0 or an integer of 1 – 2; and

G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and

15      -CH<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub> ;

- -O-CH<sub>2</sub>- ;
- -S(O)- ;
- -S(O)<sub>2</sub>- ;
- -SCH<sub>2</sub>- ;
- 20      • -S(O)CH<sub>2</sub>- ;
- -S(O)<sub>2</sub>CH<sub>2</sub>- ;
- -CH<sub>2</sub>S(O)- ; and
- -CH<sub>2</sub>S(O)<sub>2</sub>-

25      Z is N or CR<sup>4</sup>;

q is 1 or 2;

G<sup>3</sup> is a monovalent or bivalent moiety selected from the group consisting of

- 30      • lower alkyl;
- -NR<sup>3</sup>COR<sup>6</sup>;
- carboxy-substituted alkyl;

- lower alkoxy carbonyl-substituted alkyl;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- 5      • -S(O)<sub>2</sub>R<sup>6</sup>;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- 10      • -CON(R<sup>6</sup>)<sub>2</sub>;
- -S(O)<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>;
- -NO<sub>2</sub>;
- -CN;
- optionally substituted aryl;
- 15      • optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- 20      • -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -OCON(R<sup>6</sup>)<sub>2</sub>;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup>;
- 25      • -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>; and
- bivalent bridge of structure T<sup>2</sup>=T<sup>2</sup>-T<sup>3</sup> :  
     wherein  
     each T<sup>2</sup> independently represents N, CH, or CG<sup>3'</sup>; and  
     T<sup>3</sup> represents S, O, CR<sup>4</sup>G<sup>3'</sup>, C(R<sup>4</sup>)<sub>2</sub>, or NR<sup>3</sup>; wherein  
     G<sup>3'</sup> represents any of the above-defined moieties G<sup>3</sup> which are  
     monovalent; and



the terminal  $T^2$  is bound to L, and  $T^3$  is bound to D, forming a 5-membered fused ring;

A and D are CH;

B and E are CH;

5 L is CH;

with the proviso that the resulting phenyl ring bears as a  $G^3$  substituent said bivalent bridge of structure  $T^2=T^2-T^3$ ;

J is a ring selected from the group consisting of

- 10
- aryl;
  - pyridyl; and
  - cycloalkyl;

$q'$  represents the number of substituents  $G^4$  on ring J and is 0, 1, 2, 3, 4, or 5, and

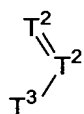
15  $G^4$  is a monovalent or bivalent moiety selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- 20 • cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- 25 • N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- 30 • carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;

- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- 5      • N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- 10     • phenyl-lower alkoxycarbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- 15     • halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- 20     • -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;
- 25     • amidino;
- guanidino;
- sulfo;
- -B(OH)<sub>2</sub>;
- optionally substituted aryl;
- 30     • optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;
- $-\text{OCO}_2\text{R}^3$ ;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- 5 •  $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-\text{CHO}$ ;
- $-\text{OCON}(\text{R}^6)_2$ ;
- 10 •  $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- $-\text{NR}^3\text{CON}(\text{R}^6)_2$ ; and
- fused ring-forming bivalent bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

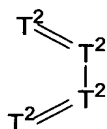
a)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^{4'}$ ; $\text{T}^3$  represents S, O,  $\text{CR}^4\text{G}^{4'}$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; wherein $\text{G}^{4'}$  represents any of the above-defined moieties  $\text{G}^4$  which are monovalent; andbinding to ring J is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

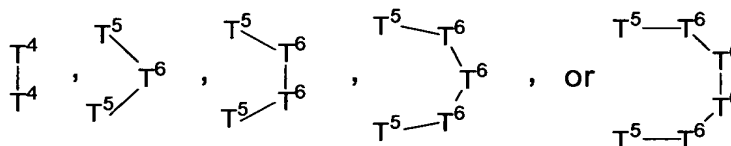
b)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^{4'}$ ; wherein $\text{G}^{4'}$  represents any of the above-defined moieties  $\text{G}^4$  which are monovalent; andwith the proviso that a maximum of two bridge atoms  $\text{T}^2$  may be N ;  
andbinding to ring J is achieved via terminal atoms  $\text{T}^2$ ; and

c)



wherein

each T<sup>4</sup>, T<sup>5</sup>, and T<sup>6</sup> independently represents O, S, CR<sup>4</sup>G<sup>4'</sup>, C(R<sup>4</sup>)<sub>2</sub>, or NR<sup>3</sup>; wherein

G4' represents any of the above-identified moieties G4 which are monovalent; and

binding to ring J is achieved via terminal atoms T<sup>4</sup> or T<sup>5</sup>;

with the provisos that:

- i) when one T<sup>4</sup> is O, S, or NR<sup>3</sup>, the other T<sup>4</sup> is CR<sup>4</sup>G<sup>4'</sup> or C(R<sup>4</sup>)<sub>2</sub> ;
- ii) a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms may contain a maximum of two heteroatoms O, S, or N; and
- iii) in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

when  $G^4$  is an alkyl group located on ring J adjacent to the linkage  $-(CR^4_2)_p-$ , and X is  $NR^3$  wherein  $R^3$  is an alkyl substituent, then  $G^4$  and the alkyl substituent  $R^3$  on X may be joined to form a bridge of structure  $-(CH_2)_{p'}-$  wherein  $p'$  is 2, 3, or 4, with the proviso that the sum of p and  $p'$  is 2, 3, or 4, resulting in formation of a nitrogen-containing ring of 5, 6, or 7 members;

and with the further provisos that:

- in G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, and G<sup>4</sup>, when two groups R<sup>3</sup> or R<sup>6</sup> are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR<sup>3</sup> to form a N-containing heterocycle of 5 – 7 ring atoms;
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy,

halogenated lower alkylthio, lower alkanoyloxy,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CHO}$ ,  $-\text{CH}_2\text{OR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{CON}(\text{R}^6)_2$ ,  $-\text{OCON}(\text{R}^6)_2$ ,  $-\text{NR}^3\text{CON}(\text{R}^6)_2$ , nitro, amidino, guanidino, mercapto, sulfo, and cyano; and

5 - when any alkyl group is attached to O, S, or N, and bears a hydroxyl substituent, then said hydroxyl substituent is separated by at least two carbon atoms from the O, S, or N to which the alkyl group is attached.

7. A compound of claim 6 wherein, in the ring comprising A, B, D, E, and L and a  
10 bivalent bridge of structure  $\text{T}^2=\text{T}^2-\text{T}^3$ , the terminal  $\text{T}^2$  represents N and the  $\text{T}^3$  unit of said bridge represents S, O,  $\text{CR}^4_2$ , or  $\text{NR}^3$ .

8. A pharmaceutical composition comprising a compound of claim 6 and a  
15 pharmaceutically acceptable carrier.

15

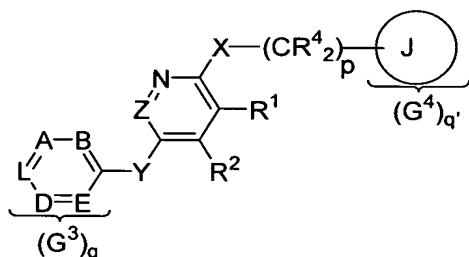
9. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to said mammal an amount of a compound of claim 6 which is effective to treat said condition.

20

10. The method of claim 9, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid,  
25 erythema multiforme, and dermatitis herpetiformis.

25

11. A compound having the generalized structural formula

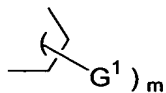


30

wherein

$R^1$  and  $R^2$  :

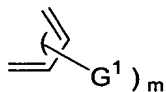
- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



5

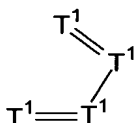
wherein binding is achieved via the terminal carbon atoms;

- iii) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms;

- iv) together form a bridge of structure

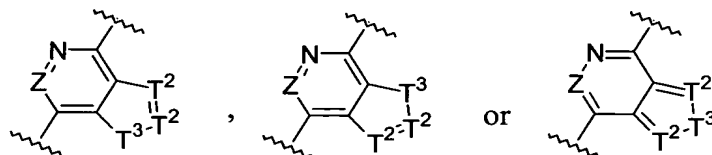


10

wherein one or two ring members  $T^1$  are N and the others are CH or  $CG^1$ , and binding is achieved via the terminal atoms; or

- v) together form a bridge containing two  $T^2$  moieties and one  $T^3$  moiety, said bridge, taken together with the ring to which it is attached, forming a bicyclic of structure

15



wherein

each  $T^2$  independently represents N, CH, or  $CG^1$ ; and  
 $T^3$  represents S, O,  $CR^4G^1$ ,  $C(R^4)_2$ , or  $NR^3$ ;

20

and wherein

$m$  is 0 or an integer 1 – 4; and

25

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;

- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- 5      • lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- 10      • N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- 15      • phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- 20      • N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- 25      • phenyl-lower alkoxycarbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- 30      • halogenated lower alkoxy;
- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- 5      • -CON(R<sup>6</sup>)<sub>2</sub> ;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub> ;
- -CN;
- amidino;
- 10      • guanidino;
- sulfo;
- -B(OH)<sub>2</sub> ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- 15      • optionally substituted saturated heterocyclyl;
- optionally substituted saturated heterocyclalkyl;
- optionally substituted partially unsaturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclalkyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- 20      • optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- 25      • -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub> ;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup> ;
- -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>

30      R<sup>3</sup> is H or lower alkyl;

R<sup>6</sup> is independently selected from the group consisting of



- H;
- alkyl;
- cycloalkyl;
- optionally substituted aryl; and
- 5   • optionally substituted aryl lower alkyl;
- lower alkyl-N(R<sup>3</sup>)<sub>2</sub>; and
- lower alkyl-OH;

R<sup>4</sup> is H, halogen, or lower alkyl;

10

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NR<sup>3</sup>;

15

Y is selected from the group consisting of

- lower alkylene;
- -CH<sub>2</sub>-O-;
- -CH<sub>2</sub>-S-;
- -CH<sub>2</sub>-NH-;
- 20   • -O-;
- -S-;
- -NH-;
- -(CR<sup>4</sup>)<sub>n</sub>-S(O)<sub>p</sub>-(5-membered heteroaryl)-(CR<sup>4</sup>)<sub>s</sub>-;
- -(CR<sup>4</sup>)<sub>n</sub>-C(G<sup>2</sup>)(R<sup>4</sup>)-(CR<sup>4</sup>)<sub>s</sub>-;

25

wherein

n and s are each independently 0 or an integer of 1 – 2; and

G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and  
-CH<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>;

- -O-CH<sub>2</sub>-;
- 30   • -S(O)-;
- -S(O)<sub>2</sub>-;
- -SCH<sub>2</sub>-;

30

- $-\text{S}(\text{O})\text{CH}_2-$  ;
- $-\text{S}(\text{O})_2\text{CH}_2-$  ;
- $-\text{CH}_2\text{S}(\text{O})-$  ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

5

Z is  $\text{CR}^4$ ;

q is 1 or 2;

10

$\text{G}^3$  is a monovalent or bivalent moiety selected from the group consisting of

- $-\text{NR}^3\text{COR}^6$ ;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;

15

- $-\text{OR}^6$ ;
- $-\text{SR}^6$ ;
- $-\text{S}(\text{O})\text{R}^6$ ;
- $-\text{S}(\text{O})_2\text{R}^6$ ;
- $-\text{OCOR}^6$ ;
- $-\text{COR}^6$ ;

20

- $-\text{CO}_2\text{R}^6$ ;
- $-\text{CH}_2\text{OR}^3$ ;
- $-\text{CON}(\text{R}^6)_2$  ;
- $-\text{S}(\text{O})_2\text{N}(\text{R}^6)_2$  ;
- $-\text{NO}_2$ ;

25

- $-\text{CN}$ ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;

30

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;

- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -OCON(R<sup>6</sup>)<sub>2</sub>;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup>;
- -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>; and
- bivalent bridge of structure T<sup>2</sup>=T<sup>2</sup>-T<sup>3</sup>

wherein

each T<sup>2</sup> independently represents N, CH, or CG<sup>3'</sup>; and

T<sup>3</sup> represents S, O, CR<sup>4</sup>G<sup>3'</sup>, C(R<sup>4</sup>)<sub>2</sub>, or NR<sup>3</sup>; wherein

G<sup>3'</sup> represents any of the above-defined moieties G<sup>3</sup> which are monovalent; and

the terminal T<sup>2</sup> is bound to L, and T<sup>3</sup> is bound to D, forming a 5-membered fused ring;

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

a) the total number of N atoms in the ring containing A, B, D, E, and L is 0, 1, 2, or 3; and

b) when L represents CH and any G<sup>3</sup> is a monovalent substituent, at least one of A and D is an N atom; and

c) when L represents CH and a G<sup>3</sup> is a bivalent bridge of structure T<sup>2</sup>=T<sup>2</sup>-T<sup>3</sup>, then A, B, D, and E are also CH;

J is a ring selected from the group consisting of

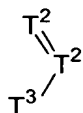
- aryl;
- pyridyl; and
- cycloalkyl;

q' represents the number of substituents G<sup>4</sup> on ring J and is 0, 1, 2, 3, 4, or 5, and

G<sup>4</sup> is a monovalent or bivalent moiety selected from the group consisting of

- $-N(R^6)_2$  ;
- $-NR^3COR^6$  ;
- halogen;
- alkyl;
- 5      • cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- 10     • N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- 15     • carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- phenyl lower alkoxy-carbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- 20     • N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- 25     • carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- phenyl-lower alkoxy-carbonyl-substituted alkylamino;
- $-OR^6$ ;
- $-SR^6$ ;
- 30     •  $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;

- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- 5     • -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- 10    • -CN;
- amidino;
- guanidino;
- sulfo;
- -B(OH)<sub>2</sub>;
- 15    • optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- 20    • optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- 25    • -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub>;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup>;
- -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>; and
- fused ring-forming bivalent bridges attached to and connecting adjacent
- 30       positions of ring J, said bridges having the structures:
- a)



wherein

each  $T^2$  independently represents N, CH, or  $CG^{4'}$ ;

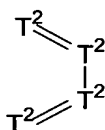
$T^3$  represents S, O,  $CR^4G^{4'}$ ,  $C(R^4)_2$ , or  $NR^3$ ; wherein

5

$G^{4'}$  represents any of the above-defined moieties  $G^4$  which are monovalent; and

binding to ring J is achieved via terminal atoms  $T^2$  and  $T^3$ ;

b)



10

wherein

each  $T^2$  independently represents N, CH, or  $CG^{4'}$ ; wherein

$G^{4'}$  represents any of the above-defined moieties  $G^4$  which are monovalent; and

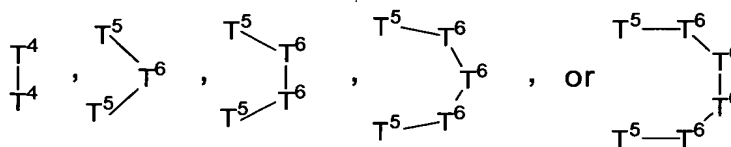
with the proviso that a maximum of two bridge atoms  $T^2$  may be N ;

15

and

binding to ring J is achieved via terminal atoms  $T^2$ ; and

c)



wherein

20

each  $T^4$ ,  $T^5$ , and  $T^6$  independently represents O, S,  $CR^4G^{4'}$ ,  $C(R^4)_2$ , or  $NR^3$ ; wherein

$G^{4'}$  represents any of the above-defined moieties  $G^4$  which are monovalent; and

binding to ring J is achieved via terminal atoms  $T^4$  or  $T^5$  ;

25

with the provisos that:

i) when one  $T^4$  is O, S, or  $NR^3$ , the other  $T^4$  is  $CR^4G^{4'}$  or  $C(R^4)_2$  ;

ii) a bridge comprising  $T^5$  and  $T^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and

iii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

5 when  $G^4$  is an alkyl group located on ring J adjacent to the linkage  $-(CR^4)_p-$ , and X is  $NR^3$  wherein  $R^3$  is an alkyl substituent, then  $G^4$  and the alkyl substituent  $R^3$  on X may be joined to form a bridge of structure  $-(CH_2)_{p'}$  - wherein  $p'$  is 2, 3, or 4, with the proviso that the sum of p and  $p'$  is 2, 3, or 4, resulting in formation of a nitrogen-containing ring of 5, 6, or 7 members;

10

and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^3$  or  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 – 7 ring atoms;

15

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy,  $-CO_2R^3$ ,  $-CHO$ ,  $-CH_2OR^3$ ,  $-OCO_2R^3$ ,  $-CON(R^6)_2$ ,  $-OCON(R^6)_2$ ,  $-NR^3CON(R^6)_2$ , nitro, amidino, guanidino, mercapto, sulfo, and cyano; and

20

25 - when any alkyl group is attached to O, S, or N, and bears a hydroxyl substituent, then said hydroxyl substituent is separated by at least two carbon atoms from the O, S, or N to which the alkyl group is attached.

30

12. A compound of claim 11 wherein  $R^4$  is H.

13. A pharmaceutical composition comprising a compound of claim 11 and a pharmaceutically acceptable carrier.

14. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to said mammal an amount of a compound of claim 11 which is effective to treat said condition.

5

15. The method of claim 14, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

10

16. A compound selected from the group consisting of examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 27, 28, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 82A, 82B, 82C, 82D, 85, 88, 89, 93, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, and 112.

15